Testimony by
Sanford N. Cohen, MD
for the
American Academy of Pediatrics

Before the Subcommittee on Health and Environment

House Commerce Committee
U.S. House of Representatives

on

Reauthorization of the Prescription Drug User Fee Act and

Food and Drug Administration Reform

April 23, 1997

Good afternoon. I am Sanford N. Cohen, MD, a pediatrician and Associate Director of the National Institute for Environmental Health Services at Wayne State University. On behalf of the American Academy of Pediatrics, I am pleased with the opportunity to provide information to the Subcommittee on Health and the Environment on several issues of critical concern to our membership. The Academy is an organization of 53,000 pediatricians dedicated to the health, safety, and well-being of infants, children, adolescents, and young adults. Since its establishment in 1930 the Academy has been a strong and constant voice for the nation's most vulnerable population -- children.

Thoughtful Congressional review of the Food and Drug Administration opens possibility for significant advances to the direct benefit of pediatric patients (ages newborn through 18 years). The Academy offers its expertise regarding children, as the Congress embarks on its journey to strengthen the FDA. We strongly urge that throughout this discussion and debate, pediatric populations are included as an integral component, not simply an after-thought, in the changes that are sought.

A critical issue and a high priority for pediatricians during the past 30 years has been the approval and labeling of medications for use by infants, children and adolescents. It is shocking to note that few drugs -- only approximately 20 percent of all drugs marketed in the United States -- have been labeled for use by infants and children. Eighty percent or more of drugs approved since 1962 have been approved and labeled for use in adults with a disclaimer in the labeling that they are not approved for use by children.

Congress has recognized the need to address this issue. In the 104th Congress, identical bills were introduced in the House and Senate -- the Better Pharmaceuticals for Children Act -- by Representative Jim Greenwood and Senator Nancy Kassebaum, respectively. The Academy applauds the commitment of members of Congress to rectify this extraordinarily problematic situation and looks forward to continuing efforts this Congress.

BACKGROUND:

Approval of a drug for human use requires proof of efficacy and safety for its specific intended use in human beings established by well controlled clinical trials. Once approved for specific indications, the drug is labeled for interstate commerce. The labeling contains the approved

prescribing information including indications, contraindications, precautions, warnings, adverse reactions, and dosage recommendations.

The Kefauver-Harris amendments to the Food and Drug Act passed in 1962 require that drugs be demonstrated by well-controlled studies to be effective for their intended uses as well as safe. While this provision has been applied to approval of drugs for use by adult patients it has not been extended to pharmaceuticals used by infants and children in the labeling of a majority of drugs. This is particularly ironic since several key Food and Drug statutes were passed in the aftermath of therapeutic catastrophes involving children. The tragic deaths of 107 children from ingestion of elixir of sulfanilamide brought about the passage of the Federal Food, Drug and Cosmetic Act of 1938, and later the tragic malformations of infants caused by maternal use of thalidomide during pregnancy led to the 1962 Kefauver amendments to the Act.

Lack of pediatric labeling does not mean that the drugs are necessarily harmful, ineffective, or contraindicated for children but simply that the clinical trials which satisfy the FDA requirements for labeling were not conducted with children. Because of this, children have not shared in

therapeutic advances to the extent adult patients have nor have they been provided the same protections afforded adult patients under the 1962 Kefauver-Harris amendments to the Food and Drug statutes. Though there has been modest progress in the labeling of marketed drugs for pediatric use, it remains sporadic and incompletely addressed.

Many reasons have been advanced for not studying and labeling drugs for use by children and adolescents, but the leading issues are regulatory impediments, economic disincentives, and reluctance on the part of the FDA to make studies in children a requirement for a new drug unless the primary use of the drug will be for children. With the exception of antibiotics, medications for fever, vaccines, and a few other therapeutic categories, pediatric use represents a relatively small segment of the total market for a drug. Companies frequently are reluctant to expend the additional time and resources to do pediatric studies with little promise of additional market potential.

CHILDREN ARE NOT SIMPLY SMALL ADULTS

It is important to understand why drugs must be studied in children to establish their safe and effective use for children. In other words, why can't adult studies provide sufficient information for use of a drug for children? No animal model or study in adults adequately predicts the effect of drugs on children of various ages and stages of development. The dynamics of growth and maturation of various organs, the changes in metabolism throughout infancy and childhood, changes in body proportions, and other developmental changes result in significant differences between children and adults. As a result, the elimination of drugs from a child's system, the dosage required and the safety and effectiveness of a pharmacologic agent need to be studied at critical developmental stages in the pediatric population.

Even within the pediatric population there is great diversity. There may be a need to study the same drug in several pediatric groups (i.e., neonates, infants, young children and adolescents) in order to determine drug efficacy, dosing, toxicity, and appropriate formulations for each subpopulation.

OFF-LABEL USES OF DRUGS IN CHILDREN AND ADOLESCENTS

An off-label use, also known as an "unapproved" use of an approved drug, refers to a use that is not included or that is disclaimed in the approved labeling. It is important to emphasize that "unapproved use" or "off-label" use does not imply an improper or illegal use. Indeed, this off-label use may represent the only, or best, treatment available for a specific illness in a child.

As mentioned, only a minority of currently marketed drugs have undergone pediatric clinical trials and have approved labeling for use in children. These include common antimicrobial agents, medications for fever, vaccines and some asthma and allergy medications. However, most drugs used to treat illnesses in children have never been formally tested or approved for pediatric use and lack even basic dosage recommendations for children in their labeling. These include such routinely used medications as dopamine (used to treat shock), cisapride (used to treat abnormal regurgitation of stomach contents in infants and small children), ketorolac (the only available injectable non-narcotic pain reliever), midazolam (used as a sedative and to treat convulsions), and adenosine (used to treat life threatening abnormal heart beats), and others.

Lack of studies to support labeling of the majority of drugs for use by children places the physician caring for children in the untenable position of either prescribing without adequate labeling or denying pediatric patients access to potentially important therapeutic agents. When confronted with this dilemma the physician most often elects to prescribe a medication without adequate pediatric labeling. As a result, off-label use of medications has, by default, become an established standard of care for children. From the patient's perspective, infants and children frequently are exposed to medications without the benefit of adequate studies to document safety and efficacy or establish doses appropriate for their age. The AAP is currently participating in a survey, sponsored by AMGEN and the American Cancer Society to quantify the prevalence of off label prescribing by pediatricians and other physicians.

A related problem is that medications not approved for use by children are not manufactured in dosage forms which can be readily administered to children. For example, many medications are provided in capsule or tablet forms which cannot be swallowed by small children and/or are not available in small enough dosage increments to give the proper dose to children.

CHILDREN REMAIN THERAPEUTIC ORPHANS

Despite efforts by FDA, few advances have been made over the last several decades to secure drug labeling for children. An examination of new molecular entities, which represent the most innovative new medications, approved by the FDA from 1984 through 1995 showed that approximately 80% of these medications were approved without labeling for children, although many of them are widely used to treat children's illnesses. An AAP survey of the 25 new drugs approved by the FDA in 1995, indicated that only three had pediatric labeling. The sponsors of 9 have indicated that pediatric studies are in progress or will done in the future, while sponsors of the remaining 14 drugs have indicated studies are not needed, since it is not likely that those drugs will be used for children. However, several of these 14 drugs undoubtedly will be used for children. For example, the sponsor of dirithromycin, a new macrolide antibiotic approved in 1995, has indicated a pediatric study is not needed or planned although it is highly likely this antibiotic will be used by physicians to treat infections in children as well as adults.

Drugs which need to be labeled for pediatric use may be divided into 3 categories based on their position in the approval process and market place: 1) new drugs in clinical trials, not yet

approved for general marketing; 2) drugs approved for adult use but not labeled for children and still under patent protection; and 3) drugs labeled for adult but not pediatric use which are off-patent and may be marketed as generic products by multiple companies. There is at least some potential economic incentive to include pediatric clinical trials in the premarketing development of new drugs. However, once a drug is marketed for an adult indication, the economic incentive to do additional studies to include pediatric labeling is markedly reduced because the drug may be prescribed off label. In the case of drugs which are off patent, there is absolutely no economic incentive to invest in studies to expand labeling because a single sponsor can no longer benefit from such an investment due to lack of exclusivity protection of the drug.

FDA EFFORTS AT PEDIATRIC LABELING

In 1979 FDA published regulations pertaining to the specific content and format of prescription drug labeling that stipulate that pediatric labeling be based on adequate, well-controlled studies involving children. The intention of these regulations was to encourage drug labeling that would regularly provide adequate information about the use of drugs in children. However, the result was not more adequately labeled drugs; rather labels simply state that the drug's safety and

effectiveness in children have not been established. Eighty percent of the prescription drugs currently marketed in the United States are labeled with such disclaimers.

In an attempt to remedy this situation the FDA published regulations on December 13, 1994, aimed at increasing pediatric information in drug labeling and facilitating addition of pediatric indications to drug labeling. The 1994 regulations recognize several methods of establishing substantial evidence to support pediatric labeling claims. These include 1) allowing inclusion of published pediatric information in the labeling and 2) approval of pediatric use based on adult efficacy studies where the disease for which the drug is to be used is substantially the same in children and adults thereby allowing pediatric studies to focus on dosing and safety data for children. The regulations respond to concerns that current prescription drug labeling too often does not contain adequate information about the uses of drugs for children and are meant to provide the physician with more complete and useful information when prescribing for children.

Though the new regulations have been in effect for almost two years, it is not yet apparent that they have resulted in any increase in new drug labeling for children. To further illustrate the lack movement on pediatric labeling based on the 1994 regulations, on December 30, 1996, the FDA granted a request by the pharmaceutical industry for an extension for the requirement for drug sponsor to reexamine existing data to determine whether the "pediatric use" section can be modified. On November 6, 1996, FDA sent a letter to 250 manufacturers asking them to notify the agency whether and when they intended to file supplements. Only 80 manufacturers responded, of which about half indicated they will submit a supplement. It is important to note that the information they may submit could simply state that safety and efficacy has not been established in the pediatric population.

FDA REFORM EFFORTS:

As noted previously, because so few drugs are labeled for pediatric populations physicians must rely heavily on off-label uses. Efforts underway to expand the dissemination of peer-reviewed information to medical professionals are viewed with interest. However, provisions

being discussed to expand the dissemination of information of off label uses across the board are broad and troubling. The Academy offers the following observations:

- With only 20 percent of drugs having pediatric labels, children already are at an extreme disadvantage in not having pediatric clinical studies performed on drugs. Allowing pharmaceutical companies to directly provide information to physicians and other health professionals for promising pediatric off label uses may substantially reduce the incentive for drug companies to conduct the scientific tests necessary for the use of a drug for new indications. It will potentially impact the pediatric population in a significant and direct manner by weakening secondary approval efficacy trials. This will reduce the information available for clinical decision-making.

x

- Published studies in peer reviewed journals may be limited in their scope (e.g., number of subjects in study, type of data that is collected, interaction of drug with other compounds). To extrapolate recommendations from a single study and disseminate it widely may

generate the perception that this is the appropriate standard for that drug when in fact, the study may be an element of a much larger, more comprehensive review.

x

- Dissemination of information is based upon whether it is allowed to be published in a journal. Journals receive numerous articles for publication in each issue but only a limited number are published. Other studies that may be important to the overall issue may never be published but could provide valuable information -- either supporting or refuting -- the published study. Further, the journal reviewers may not be expert in the specific field which the articles addresses.

x

- Pediatricians (experts in child health) are forced to rely on limited information in prescribing medications to the pediatric population. The risk to children is increased when non-pediatrician practitioners prescribe drugs to those populations. Given continued efforts to expand the medication prescribing authority to non-physician health professionals, the risk to children and adolescents may become even greater.

x

- Cancer drugs can be discussed as a separate entity and should not be accepted as the standard from which generalizations should be made. FDA has a different, more streamlined approach to studies and approval for this class of drugs because they are recognized as different. In addition "off label" pediatric uses are controlled by recognized pediatric oncology study groups.

RECOMMENDATIONS:

While we commend the efforts of the FDA at internally reforming the agency, we are concerned that the regulations of December, 1994 meant to encourage the inclusion of pediatric data in FDA-approved labeling, have failed to achieve their goal. The American Academy of Pediatrics believes additional steps must be taken to augment the FDA initiatives and supports the following measures to overcome some of the principal obstacles to labeling medications for children:

- AAP recommends that Congress urge the FDA to exercise their statutory authority and responsibility to make studies in appropriate pediatric populations a requirement during clinical trials of each new drug having a potential for use by children, unless it is determined

by a panel of experts in pediatric medicine that there will be no use of that drug for children and/or adolescents.

- Recognizing that current regulations allow for industry to provide physicians with requested information for off-label uses, the Academy recommends that legislative efforts to expand dissemination of information of off-label uses of drugs beyond current regulations exclude the pediatric population. Any dissemination policy should include the following provisions:

x

x -- For those drugs without labeling for pediatric populations, drug manufacturers may not disseminate off-label use information about pediatric populations, unless such information is specifically requested by the physician;

-- For those drugs with pediatric age specific labeling, drug manufacturers may not disseminate off-label use information about age

populations not specified in the label, unless such information is specifically requested by the physician.

- Congress should require that a pediatric representative be included in all FDA Advisory Committees. Currently, women and minorities have confirmed representation but the pediatric perspective is missing.

- The Congress should establish an independent panel of experts in pediatric medicine, nominated by the American Academy of Pediatrics, the Pediatric Pharmacology Research Unit Network, U.S. Pharmacopoeia with authority to:

  -- advise FDA which new drugs might have pediatric applications and the types of studies required in specific pediatric populations;

  -- determine the need for studies of specific marketed drugs for the pediatric population;

  -- advise the FDA on the approvability of specific NDA's;

- FDA should establish age definitions for children to be used for regulatory purposes as the standard throughout the Agency. The AAP recommends the following:
    - child means a neonate, infant, toddler, young child, child, or adolescent;
    - neonate means a child from birth to the age of one month (28 days);
    - infant means a child from the age of one month to the age of one year;
    - toddler means a child from the age of one year to the age of two years;
    - young child means a child from the age of two years to the age of five years;
    - child means a child from the age of five years to the age of 12 years;
    - adolescent means a child from the age of 12 years to the age of 18 years.

- The FDA should, in consultation with the independent panel of experts in pediatric medicine, develop, prioritize and publish a compendium of already approved and patented drugs, as well as drugs whose patents have expired, for which pediatric labeling is necessary.

- The American Academy of Pediatrics supports consideration of proposals to provide economic incentives, if necessary, to companies which conduct pediatric studies and provide

pediatric dosage formulations, for new drugs as well as already approved and off-patent drugs. Consideration should be given to patent extension for companies who complete pediatric studies which lead to pediatric labeling.

The American Academy of Pediatrics is pleased to work with Members of Congress to develop the best and most far-reaching protections for infants, children, adolescents and young adults. We welcome the opportunity to continue this dialogue.

EXECUTIVE SUMMARY

For over 30 years, the American Academy of Pediatrics (AAP) has actively fought for approval and labeling of medications for use by infants, children and adolescents. AAP has met with limited success. Congress has an opportunity to make a significant advance which will directly benefit children.

THERE IS A CRITICAL NEED FOR PEDIATRIC STUDIES IN DRUGS

Only approximately 20 percent of all drugs marketed in the United States have been labeled for use by children. Eighty percent or more of drugs approved since 1962 have been approved and labeled for use in adults with a disclaimer that they are not approved for use by children.Despite various attempts by FDA to address this problem, the proportion of approved new drugs labeled for children has not changed during the past decade.

Absence of studies to support labeling of the majority of drugs for children places the physician in the untenable position of either prescribing without adequate labeling or denying pediatric patients access to important therapeutic agents. When confronted with this dilemma the physician invariably prescribes the medication that does not have a specific usage label for children, known as "off-label". As a result, off-label use of medications has, by default, become an established standard of care for children. Infants and children frequently are exposed to medications without the benefit of adequate studies to document safety and efficacy or to establish doses appropriate for their age.

RECOMMENDATIONS:

- The American Academy of Pediatrics recommends that Congress urge the FDA to exercise their statutory authority and responsibility to make studies in appropriate pediatric populations a requirement during clinical trials of each new drug having a potential for use by children, unless it is determined by a panel of experts in pediatric medicine that there will be no use of that drug for children and/or adolescents.

I. Recognizing that current regulations allow for industry to provide physicians with requested information for off-label uses, the Academy recommends that legislative efforts to expand dissemination of information of off-label uses of drugs beyond current regulations exclude the pediatric population. Any dissemination policy should include the following provisions:

a) -- For those drugs without labeling for pediatric populations, drug manufacturers may not disseminate off-label use information about pediatric populations, unless such information is specifically requested by the physician;

-- For those drugs with pediatric age specific labeling, drug manufacturers may not disseminate off-label use information about age populations not specified in the label, unless such information is specifically requested by the physician.

I. Congress should require that a pediatric representative be included in all FDA Advisory Committees. Currently, women and minorities have confirmed representation but the pediatric perspective is missing.

I. The Congress should establish an independent panel of experts in pediatric medicine, nominated by the American Academy of Pediatrics, the Pediatric Pharmacology Research Unit Network, U.S. Pharmacopoeia with authority to:

-- advise FDA which new drugs might have pediatric applications and the types of studies required in specific pediatric populations;

-- determine the need for studies of specific marketed drugs for the pediatric population;

-- advise the FDA on the approvability of specific NDA's;

I. FDA should establish age definitions for children to be used for regulatory purposes as the standard throughout the Agency.

I. The FDA should, in consultation with the independent panel of experts in pediatric medicine, develop, prioritize and publish a compendium of already approved and patented drugs, as well as drugs whose patents have expired, for which pediatric labeling is necessary.

I. The American Academy of Pediatrics supports consideration of proposals to provide economic incentives, if necessary, to companies which conduct pediatric studies and provide pediatric dosage formulations, for new drugs as well as already approved and off-patent drugs. Consideration should be given to patent extension for companies who complete pediatric studies which lead to pediatric labeling.